UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, KBI INC. and KBI-E INC., Plaintiffs and Counterclaim-Defendants, v. HANMI USA, INC., HANMI PHARMACEUTICAL CO., LTD., HANMI FINE CHEMICAL CO., LTD. and HANMI HOLDINGS CO., LTD., Defendants and Counterclaim-Plaintiffs.	Civil Action No. 3:11-CV-00760-JAP-TJB Judge Joel A. Pisano Magistrate Judge Tonianne J. Bongiovanni

DECLARATION OF DR. STEPHEN G. DAVIES ON CLAIM CONSTRUCTION

I, STEPHEN G. DAVIES, a Citizen of Great Britain, DECLARE AS FOLLOWS:

I. EDUCATIONAL BACKGROUND AND QUALIFICATIONS

1. I am the Waynflete Professor of Chemistry at the University of Oxford, where I have been teaching since 1980. From 2006–2011 I was also Chairman of the Depatrment of Chemistry at Oxford. My responsibilities included all aspects of academic leadership and day to day management of one of the largest chemistry departments in the world. In addition to my teaching duties, I have supervised more than 100 graduate students and 100 post-doctoral fellows in the area of organic and organometallic chemistry with particular emphasis on all aspects of stereochemistry.

2. I earned a B.A. degree in 1973 and a D. Phil. Degree in 1975, both in Chemistry from the University of Oxford. I received a D.Sc. degree in Chemistry from the University of Paris in 1980.

3. I have held numerous editorial appointments, a list of which can be found in my CV, attached as Exh. 1. Additionally, I am the founder and Editor in Chief of Tetrahedron Asymmetry, a leading international journal which reports advances in knowledge of all aspects of stereochemistry in organic, inorganic, organometallic, physical and bioorganic chemistry. As Editor in Chief, I have read nearly every submission to that journal, including those not accepted for publication, over the last 22 years. I have authored close to 500 publications and have given scores of research lectures. A list of my publications may also be found in Exh. 1. I have also received numerous awards in my area of expertise, including: Royal Society of Chemistry Perkin Prize 2011; Prize Lectureship of the Society of Synthetic Organic Chemistry, Japan (1998); Royal Society of Chemistry, Stereochemistry Award (1997); Tilden Lecture Award, Royal Society of Chemistry (1996); Royal Society of Chemistry Alfred Bader Award (1989);

Pfizer Award for Chemistry (1988); Royal Society of Chemistry Award for 0rganometallic Chemistry (1987); Pfizer Award for Chemistry (1985); and Hickinbottom Fellowship (1984).

4. My research interests are in the area of the stereochemical aspects of organic chemistry, and in particular, the preparation of enantiomerically pure (i.e. "homochiral") materials. My particular interests are the asymmetric and stereoselective synthesis of homochiral compounds.

5. Because of my expertise in the preparation of homochiral compounds, in the late 1980's and early 1990's I received numerous requests from scientists and pharmaceutical companies seeking assistance in obtaining stereochemically pure compounds of interest. In some cases, these individuals had tried and failed to obtain the desired compound. In other instances, they did not know where to begin.

6. Based on my experience as a consultant, I determined that there was a strong need to provide the scientific community with expertise in the area of single enantiomer preparation. Every attempt at preparing single enantiomers is unique, and the need could not be filled by drafting a textbook or treatise describing all of the various known methods of producing enantiomers of racemic compounds. Likewise, it was insufficient to point people to product literature. This was not because the scientific community was unaware of the available techniques, but rather because of the failure to be able to identify a successful technique in a given case and to apply it to reach the desired goal.

7. As a result, along with several others, I founded Oxford Asymmetry, Ltd. in 1992, which became a division of Oxford Asymmetry International plc. Our mission was to provide pharmaceutical companies with homochiral compounds of interest on any desired scale, from small amounts for biological evaluation and research, to commercial quantities. The company

was focused on the preparation of compounds with high enantiomeric purities. The company specialized in the following methods of achieving this: (1) using single enantiomer "chiral pool" starting materials; (2) asymmetric synthesis; and (3) chiral separations by various methods (resolutions).

8. The company grew from 3 employees to 250 employees by the time it was sold, demonstrating the high demand and need for its services. This overwhelming growth also demonstrated that scientists and pharmaceutical companies could not rely on textbooks and product literature to obtain the requisite knowledge to obtain the desired compounds. Again, the available literature did not teach how to obtain all enantiomers of potential pharmaceutical interest.

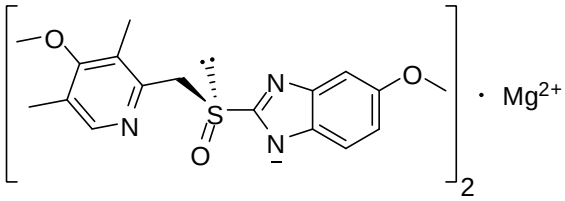
9. In 1995 I founded Oxford Diversity, Ltd., which used methods of combinatorial chemistry to produce large numbers of organic compounds that companies would then screen for biological activities. In 1998 this company was combined with Oxford Asymmetry to form Oxford Asymmetry International, plc.

10. In 2003 I founded another company, VASTox, plc (now Summit Corporation plc). VASTox is an acronym for Value Added Screening Technologies Oxford. This company was focused on chemical genomics and offered unique drug discovery and toxicology services to the pharmaceutical industry and developed a new strategy for drug discovery. Pharmaceutical companies traditionally have used a 'Gene-to-Screen' approach in which genomics technologies are employed to find new targets for drugs to treat human disease. Once the targets are located, vast numbers of chemical compounds are screened to identify drug prototypes that modulate the disease target. However, this approach has been proven largely ineffective except for a handful of new drug launches. VASTox's 'Screen-to-Gene' approach reverses this process. Rather than

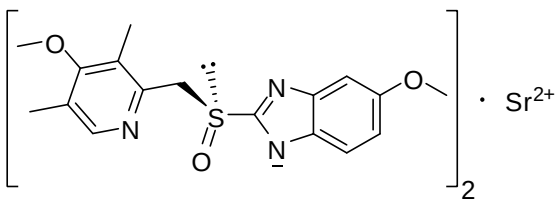
starting with the disease, clients' chemical libraries are probed in phenotypic screens, which allows the rapid and simultaneous identification of both the molecular targets for human disease as well as suitable drug prototypes. VASTox comprised two parts, the first was chemical synthesis and the second was genomics. However, even though it was not the core of our business, we were still hired to assist pharmaceutical companies in preparing compounds with high enantiomeric purities. Today Summit plc (formerly VASTox plc) is concentrating on developing its own pharmaceuticals, for instance to treat the orphan disease Duchenne Muscular Dystrophy.

II. SCOPE OF DECLARATION

11. I understand that this litigation involves the Plaintiffs' ("AstraZeneca's") U.S. Patents Nos. 5,714,504 (the " '504" patent) and 5,877,192 (the " '192" patent), which cover AstraZeneca's Nexium® product for treating gastric acid-related conditions. The active ingredient in Nexium® is esomeprazole magnesium:



12. I understand that the Defendants ("Hanmi") have applied for permission from the U.S. Food and Drug Administration to sell a generic version of Nexium® that uses esomeprazole strontium prior to the expiration of the '504 and '192 patents:



13. I have been asked by counsel for AstraZeneca to provide my opinion on the knowledge and understanding of the person of ordinary skill in the art ("person of ordinary skill"), and the understanding such a person would have of the following terms from the claims of the '504 patent:

- "alkaline salt;"
- "the (–)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethy1-2-pyridinyl)methyl]sulfinyll-lH-benzirnidazole" alone and as modified by "optically pure;"

and the '192 patent:

- "pharmaceutically acceptable salt;" and
- "consisting essentially of the (–)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole."

14. In preparing this declaration, I have reviewed the '504 and '192 patents as well as the prosecution history of each, the parent applications and prosecutions histories leading to the '504 and '192 patents, the parties' Joint Claim Construction and Prehearing Statement Exhibits A through D, and the documents attached as exhibits hereto.

15. I have testified as an expert at trial or by deposition in the cases listed at the end of the attached CV (Exh. 1). I am being paid GB£350 per hour for my time spent in study and testimony in this matter.

16. I reserve the right to prepare exhibits to summarize or support the opinions set forth below.

III. SCIENTIFIC BACKGROUND

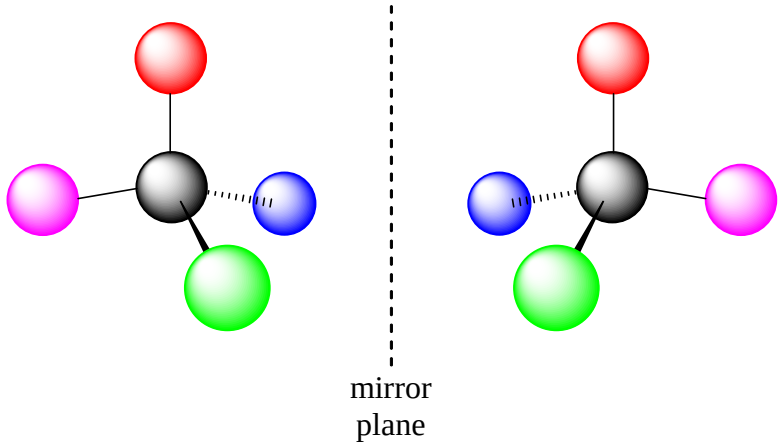
17. Molecules (compounds) are comprised of groups of atoms bonded together in a particular pattern. Molecular structures can be conveyed with words or pictures.

18. Most pharmaceutical agents belong to the class of chemicals known as organic compounds, which are typically composed of carbon (C), hydrogen (H), nitrogen (N) and oxygen

(O) atoms and sometimes contain additional elements such as sulfur (S). The atoms of each element engage in a characteristic number of bonds when they are joined with other atoms in a molecule; for example, hydrogen forms only one bond, oxygen 2, nitrogen 3 and carbon 4.

19. Organic molecules are 3-dimensional; hence simple 2-dimensional drawings may not convey all their structural complexities. In particular, molecules that share the same 2-dimensional arrangement may in fact be different forms in three dimensions. Such molecules are referred to generally as stereoisomers.

20. For example, when four groups are attached to a carbon atom (center atom below), they are arranged in a tetrahedral fashion. If the four groups are different, then there are two possible spatial orientations.

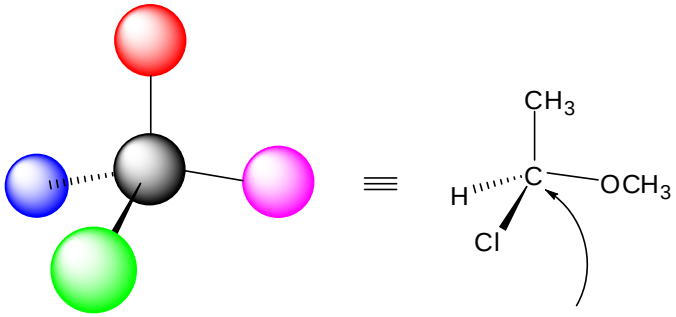


In this drawing, a solid wedge depicts an atom or group oriented toward the viewer, and a hashed wedge depicts an atom or group oriented away from the viewer.

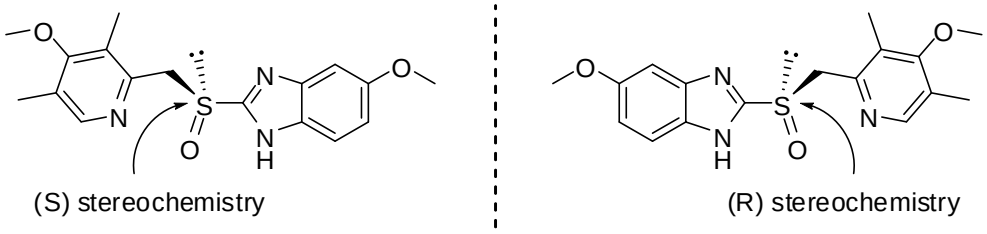
21. Although these molecules have the same connectivity, they are non-superimposable mirror images. This means that no matter how much you twist or turn these molecules, you cannot make one identical to the other without breaking and rearranging the bond connectivities. Such molecules are called “enantiomers” (stereoisomers that are mirror images).

22. This property of a molecule is known as "chirality" (taken from the Greek word for hand) because, like a person's right and left hands, enantiomers are non-superimposable mirror images of each other.

23. The carbon with four different groups attached to it is referred to as a stereogenic centre, or stereocentre. A molecule with one stereogenic centre always has two possible enantiomers.



24. Chemists characterize each enantiomer in a given pair of enantiomers based on the spatial arrangement, or configuration, of the atoms around the stereogenic atom using the symbols "(S)" and "(R)." These designations refer to the absolute configuration (the actual arrangements in 3D space) based on a standard nomenclature convention. For example, the (S) and (R) enantiomers of omeprazole (as discussed later, also referred to as the (–) and (+) enantiomers, respectively) are depicted below:



In these compounds, the stereogenic centre is the sulfur atom (the "S" atom in the depiction).

25. Chemists can also characterize each enantiomer in a given pair of enantiomers based on the fact that a solution containing one enantiomer rotates a plane of polarized light in

either a clockwise or counter-clockwise direction. A compound that rotates polarized light in this manner is referred to as an optically active compound. Optically active compounds that rotate the plane of polarized light to the right, or in a clockwise direction, are commonly described as dextro-rotatory and represented with a "(+)" symbol or the prefix "d-" for "dextro-." Compounds that rotate the plane of polarized light to the left, or in a counterclockwise direction, are described as levo-rotatory and commonly represented with a "(–)" symbol or the prefix "l-" for "levo-."

26. For a chemist, the full name for a given enantiomer reveals its chemical structure as well as its absolute configuration in 3-dimensional space ("(R)" or "(S)") and the direction in which it rotates polarized light ("(+)" or "(–)"; "d" or "l").

27. When chemists synthesize an organic compound that has a stereogenic carbon, unless specific steps are taken, the material that they obtain contains both enantiomers in equal proportions (i.e., 50% "(R)" and 50% "(S)" molecules). Such material may be generally referred to as a "racemic mixture" or "racemate."

28. A racemate does not rotate a plane of polarized light—and is therefore not optically active—because in solution the rotation caused by the (–)-enantiomer is cancelled exactly by the equal and opposite rotation of the (+)-enantiomer. Omeprazole is an example of a racemic mixture (a 50:50 mixture of the (R) and (S) enantiomers depicted above).

29. An enantiomer's (R) or (S) configuration is determined solely by its structure and bond connectivity, and is determined by a simple set of rules dependent upon the orientation in 3D space of these bonds. However, whether a molecule with an (R) configuration is dextro-rotatory or levo-rotatory (and thus classified as (d) or (1) or (+) or (–)) can only be determined after experimental testing. Likewise, a molecule that contains a stereogenic centre and that is

determined experimentally to be dextro-rotatory by the manner in which it rotates the plane of polarized light cannot be classified as (R) or (S) without knowing the 3D connectivity of a molecule through knowledge of its absolute configuration—this has to be determined separately by another means, such as X-ray crystallography. Therefore, until and unless at least one of the enantiomers is isolated and tested, a chemist would not know which way either enantiomer would rotate a plane of polarized light. Thus, the designation of (d) vs. (1) or (+) vs. (–) can only be assigned after one of the enantiomers has been isolated and tested under the appropriate conditions.

30. The "optical purity" of a mixture of enantiomers may be expressed in terms of "enantiomeric excess (e.e.)." Enantiomeric excess is the difference between the percentage amount of two enantiomers in a mixture. For example, if an enantiomerically-enriched preparation contains 97% of the (–)-enantiomer and 3% of the (+)-enantiomer, the optical purity of that preparation could be expressed as 94% e.e. (97% – 3% = 94% e.e.).

31. Should the Court determine that it would be helpful, I am prepared to provide a tutorial on principles of stereochemistry as well as scientific principles pertaining to salts, basicity and acidity. I reserve the right to prepare exhibits to support any such tutorial.

IV. OPINIONS

A. The Person of Ordinary Skill

32. Counsel has informed me that only certain claims of the '504 and '192 patents are at issue in this litigation. The asserted claims of the '504 patent (claims 1–7 and 10) are generally directed to "pharmaceutical formulation[s]" containing an "alkaline salt" of (–)-omeprazole and methods of use thereof for "inhibiting gastric acid secretion" and "treatment of gastrointestinal inflammatory disease." The asserted claims of the '192 patent (1–7, 10–19 and 21–23) are generally directed to methods for the "treatment of gastric acid related diseases" with

(–)-omeprazole "or a pharmaceutically acceptable salt thereof" and to methods for the "production of a medicament for treating gastric acid related diseases" containing the same.

33. I understand that the claims of a patent must be read from the viewpoint of a hypothetical person of ordinary skill in the art. As mentioned above, I have been asked to address claim terms that pertain to concepts of acidity/basicity, salts and stereochemistry and that relate to pharmaceutical treatments or methods of administration. In my opinion, a hypothetical person of ordinary skill in the art would have skills in both chemistry and in treating disorders of the upper gastrointestinal tract. The chemistry skills of a hypothethical person of ordinary skill in the art would in my opinion require at least a B.Sc. in chemistry and some industrial work experience in, for example, synthetic organic chemistry, including experience with salt preparation, as well as the preparation or separation of stereoisomers. I understand that Dr. Johnson has described additional attributes of this hypothetical person of ordinary skill that pertain to the treatment of diseases or disorders of the upper gastrointestinal tract.

B. '504 Patent Claim Language

1. "Alkaline salt"

34. The term "alkaline salt" appears expressly or by dependence in all of the asserted claims of the '504 patent. I understand that Hanmi interprets this term is limited to mean only those salt forms named in the patent ("Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} or $N^+(R)_4$ salt"). I disagree.

a. Ordinary Meaning

35. A "salt" is made up of positively charged ions (cations) and negatively charged ions (anions) held together in the solid state by ionic bonds. In water, the individual ions that make up a salt tend to dissociate. Common table salt (sodium chloride) is an example of a salt that is made up of positively-charged sodium cations and negatively-charged chloride anions.

36. An "alkaline salt" would ordinarily be understood to mean a salt that is basic—that is, one that generates basic solutions in water or that is generated under basic conditions. This is in contrast to an acidic salt—one that generates acidic solutions in water or is formed under acidic conditions. The term "alkaline" derives from the alkali and alkaline earth metals, Groups I and II on the periodic table, which react with water to provide basic solutions. Indeed, a person of ordinary skill would understand that suitable cations for "alkaline salts" include, at least, cations of all of the metals in Groups I and II (lithium, sodium, potassium, rubidium, caesium, beryllium, magnesium, calcium, strontium or barium) as well as ammonium, which is often considered an honorary alkaline salt because ammonia, when dissolved in water, affords a basic solution.[1]

37. In the '504 patent claims, the term "alkaline salt" is followed by "of the (–)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethy1-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole," which is (–)-omeprazole (see below). Thus, the "alkaline salt" in claim 1 is a "basic salt" (as understood above) of (–)-omeprazole.

38. (–)-omeprazole is "amphoteric," which means that it is able to form a salt either under basic conditions by loss of a proton or under acidic conditions by addition of a proton.

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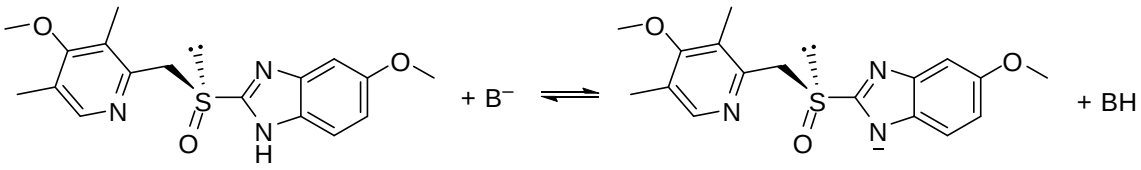
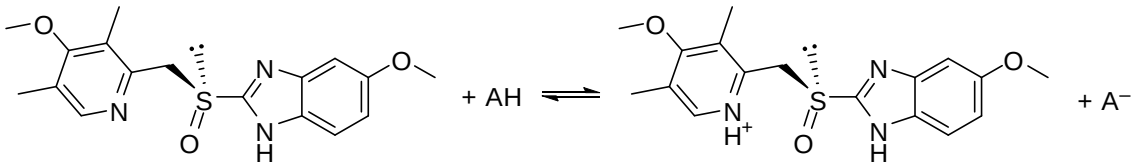
[1] See, e.g., Chambers Dictionary of Science and Technology, Revised Edition (1974): defining "alkali metals" to mean "lithium, sodium, potassium, rubidium, and caesium, all monovalent metals in the first group of the periodic system;" "alkaline earth metals" to mean "beryllium, magnesium, calcium, strontium, barium, and radium, all divalent metals in the second group of the periodic system;" "alkaline solution" to mean: "an aqueous solution containing more hydroxyl ions than hydrogen ions;" and "alkalinity" to mean: "The extent to which a solution is alkaline[, s]ee pH value." (AZ0005145462–64, Exh. 2). In chemistry, the degree of acidity or alkalinity of a solution is reflected by a numerical 'pH' scale. A pH of 7.0 is neutral. Solutions with a pH below 7.0 are acidic and solutions with a pH above 7.0 are basic (or alkaline).

39. A person of ordinary skill would understand that in order to remove a proton from (–)-omeprazole, which would introduce a negative charge, it must be treated with a base (here, shown generically as B^-):



A person of ordinary skill would also understand that the resulting salt would be basic, i.e., alkaline (only the anion of the salt is depicted here).

40. In contrast, a person of ordinary skill would understand that in order to add a proton to (–)-omeprazole, which would introduce a positive charge, it must be treated with an acid (here, shown generically as AH):



A person of ordinary skill would understand that the resulting salt would be acidic and would not consider acid addition salts of (–)-omeprazole such as that generally depicted here to be alkaline salts.

41. In addition, the patent claims are directed to pharmaceutical formulations or methods of using pharmaceutical formulations. Thus, the "alkaline salts" of (–)-omeprazole in the patent claims are those suitable for use in a pharmaceutical formulation.[2]

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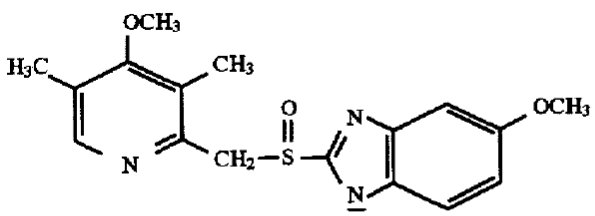
[2] As noted above, the exemplified options for cations in the alkaline salts includes "$N^+(R)_4$." "R" is defined in the '504 patent to be "an alkyl with 1–4 carbon atoms" (col. 2, l. 44), which could be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl and s-butyl (which could itself exist as either of two possible stereochemical configurations). The chemical group "$N^+(R)_4$" in the '504 patent is an ammonium group.

42. Therefore, "alkaline salt," as read in the context of the claims in which it appears, would be understood to mean a basic salt (here, a salt in which (–)-omeprazole is negatively charged) that is suitable for use in a pharmaceutical formulation. [3]

b. The '504 patent specification and prosecution history

43. I understand that Hanmi has identified the entire '504 patent and its file history, including predecessor applications, as support for its construction. For the reasons I explain below, neither the '504 patent nor its file history support Hanmi's proposed interpretation of "alkaline salt". The patent specification and file history are consistent with the ordinary meaning of "alkaline salt" discussed above.

44. For example, the "most preferred" salts of the '504 patent are structures **I** and **II** in column 3, which depict individual enantiomers of omeprazole with a negative charge (deprotonated):[4]



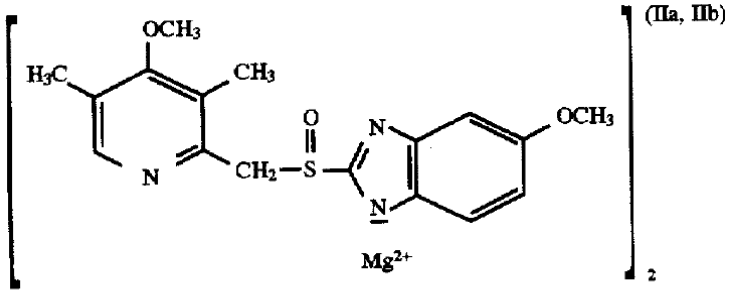
(Ia, Ib)

Nat

Ia (+)-enantiomer
Ib (–)-enantiomer

[3] I understand from counsel that Hanmi's generic Nexium® product is a salt of anionic (deprotonated, thus basic) (–)-omeprazole with Sr^{2+} (strontium) as the cation. I understand that strontium salts have previously been used clinically. See, e.g., the background discussions of prior clinical application of strontium salts as well as the list of references in Marie (1993) *J. Bone Min. Res.* 8(5): 607 (AZ0005145385–94, Exh. 3); Marie (1986) *Metabolism* 35: 547 (AZ0005144147–51, Exh. 4); and Marie (1985) *Miner. Electrolyte Metab.* 11: 5 (AZ0005145453–61, Exh. 5).

[4] While the stereocentre in these compounds is not depicted in the same manner as above for the enantiomers of omeprazole, ¶ 24, a person of ordinary skill still understands that the sulfur atom bears four distinct groups in each of the enantiomers of structures **I** and **II**.



IIa (+)-enantiomer
IIb (–)-enantiomer

As discussed above, these salts, in which an individual enantiomer of omeprazole is deprotonated, are basic, or alkaline.

45. In addition, the preparation of the "alkaline salts" of the '504 patent is described generally as involving treatment of a neutral enantiomer of omeprazole "with a base." Col. 4, ll. 51–61, l. 65 – col. 5, l. 4. Such preparation thus occurs under basic conditions, and results in an enantiomer of omeprazole that is deprotonated and anionic (and is not protonated and cationic as in an acid addition salt), just as in structures **I** and **II**.

46. Examples 1–3, 6 and 7 detail specific applications of this general procedure. In these examples, the "alkaline salts" of (–)-omeprazole are formed by deprotonation of neutral (–)-omeprazole with base (sodium hydroxide or magnesium methoxide) affording salts in which (–)-omeprazole bears a negative charge (is deprotonated).

47. In addition, all exemplary counterions for the salts of individual enantiomers of omeprazole that are mentioned throughout the specification are cationic (positively charged) meaning individual enantiomers of omeprazole must be anionic (bear a negative charge) in such salts.

48. Moreover, the specification emphasizes "the surprising high stability in alkaline conditions for the compounds of the invention," as contrasted to the "acidic conditions" employed in unsuccessful prior efforts to prepare "optically pure [individual enantiomers of]

omeprazole"—specifically noting that acidic conditions "would be devastating" for the individual enantiomers of the invention. *Compare* col. 13, l. 31 – col. 14, l. 4 (discussing the stability under alkaline conditions), to col. 1, ll. 27–42 (discussing the hazards acidic conditions present).

49. Once formed, the salts of the invention may be converted to other salts by treatment with another cation. Examples 4 and 5 demonstrate the conversion of a sodium salt to a magnesium salt of an omeprazole enantiomer by treatment of the sodium salt with magnesium chloride. It is important to note that these salts were prepared from other salts, the sodium salts of Examples 2 and 1, respectively. As noted above, the sodium salts of Examples 1 and 2 are alkaline salts that were themselves prepared under basic conditions. In addition, the cation exchange is done in solution and thus also occurs under basic conditions. Thus, all salts of the examples were originally prepared under basic conditions.

50. Each of the foregoing disclosures would reinforce the understanding of the person of ordinary skill that the "alkaline salts" of the invention are "basic" and contain (–)-omeprazole that is negatively charged.

51. In addition, the specification confirms the pharmaceutical utility for the invention throughout, reinforcing the understanding that the "alkaline salts" of (-)-omeprazole of the claims are those suitable for use in pharmaceutical compositions.

52. I understand that Hanmi interprets "alkaline salt" of claim 1 to mean only sodium, magnesium, lithium, potassium, calcium and quaternary ammonium (Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} or $N^+(R)_4$). I do not believe a person of ordinary skill would share that understanding.

53. Comparing claim 1 to dependent claim 3, and claims 6 and 7 to dependent claim 10, shows that the dependent claims expressly specify the same options for "alkaline salts" that

Hanmi has identified ("Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} or $N^+(R)_4$ salt"), while the independent claims refer simply to "alkaline salt." A person of ordinary skill would understand from the claims themselves that the "alkaline salts" in claims 1, 6 and 7 include more cations than just "Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} or $N^+(R)_4$" of dependent claims 3 and 10, as Hanmi suggests.

54. In addition, a person of ordinary skill would understand from the specification that the salt forms identified by Hanmi are merely examples:

> Alkaline salts of the single enantiomers of the invention are, as mentioned above, beside the sodium salts (compounds Ia and Ib) and the magnesium salts (compounds IIa and IIb), exemplified by their salts with Li^+, K^+, Ca^{2+} and $N^+(R)_4$[.]

Col. 5, ll. 7–11. The express language "exemplified by" conveys that the identified salt forms ("Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} or $N^+(R)_4$") are merely examples of some (not all) of the possible "alkaline salts."

55. A person of ordinary skill reviewing the '504 patent would also note the statement that "alkaline salts" of omeprazole were "described in," for example, in EP 124,495 ("EP '495"). Col. 1, ll. 17–21. EP '495 and its U.S. counterpart, U.S. Patent No. 4,738,974, are AstraZeneca patents that discuss "alkaline salts" of racemic omeprazole. Both of these patents disclose examples of counterions for "alkaline salts" of omeprazole that are not among those listed by Hanmi (e.g., a titanium counterion). (EP '495 (AZ0005144655–71, Exh. 6): p. 2, ll. 19–35; p. 5, ll. 26–27, Examples 1–10; '974 patent (AZ0001414538–43, Exh. 7): col. 1, l. 67 to col. 2, l. 23; col. 3, l. 49, Examples 1–10). These publications, and the citation to "alkaline salts" of omeprazole in EP '495 within the specification of the '504 patent, are also consistent with the ordinary meaning of "alkaline salt".

56. Hanmi has also cited to various events during the prosecution of the '504 patent to support its narrow construction. The prosecution history, however, also belies such an

understanding. For example, Hanmi cites to a January 21, 1997 Examiner Interview Summary addressing the patentability of claims, in which the Examiner states:

> A pharmaceutical formulation for oral administration of pure solid state (–) enantiomer of omeprazole Na-salt may be allowable after reviewing the data in affidavit form. . . . The scope of the claim will depend on the data submitted.

I do not believe this statement requires the narrow construction that Hanmi proposes. Indeed, in a February 18, 1997 response and amendment, the Applicants discussed and submitted a declaration disclosing:

> clinical studies which involved both the monovalent sodium salt and the divalent magnesium salt of the (–)-enantiomer of omeprazole, ***thus supporting the full scope of the genus of alkaline salts disclosed in the application and as claimed herein, as suggested by the Examiner at the interview***.

(Emphasis added.) The pending claims at the time were those that ultimately issued, and thus a person of ordinary skill would understand that the Examiner found the data on the sodium and magnesium salts sufficient to support the claims to "Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} or $N^+(R)_4$ salt[s]" as well as the broader genus of "alkaline salts."

* * *

57. In view of the above, a person of ordinary skill would understand "alkaline salt" to mean any basic salt (here, a salt in which (–)-omeprazole is negatively charged) that is suitable for use in a pharmaceutical formulation, and to not be limited to the exemplary salt forms in the specification.

2. "(–)-Enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole" alone and as modified by "optically pure"

58. The term "(–)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole" appears expressly or by dependence in all of the asserted claims of the '504 patent and is modified by "optically pure" in asserted claim 2. I

understand that the Court already construed these terms in the manner previously proposed by AstraZeneca. Should the Court decide to revisit the construction of these terms, I provide my opinion as to the meaning in the attached Appendix.

C. '192 Patent Claim Language

1. "Pharmaceutically acceptable salt"

59. The term "pharmaceutically acceptable salt" appears expressly or by dependence in all of the asserted claims of the '192 patent. I understand that Hanmi interprets the term "pharmaceutically acceptable salt" to mean only those salt forms specifically named in the '504 patent ("Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} or $N^+(R)_4$ salt"), or alternatively that the term embraces both "alkaline salts" and "acid addition salts." I disagree with both of these constructions.

a. Ordinary Meaning

60. As discussed above, a "salt" is made up of cations and anions held together in the solid state by ionic bonds.

61. In the claims of the '192 patent, "pharmaceutically acceptable salt" always modifies the chemical name for (–)-omeprazole. Thus, the "salt" in question is a salt of (–)-omeprazole.

62. A "pharmaceutically acceptable salt" would be understood be one that is suitable for pharmaceutical administration. This understanding would be reinforced by the claim language referencing the administration of the salts of (–)-omeprazole in various methods of treatment.

b. <u>The '192 patent specification and prosecution history</u>

63. I understand that Hanmi has identified the entire '504 and '192 patents as well as the file history of each, including predecessor applications, in support of its two constructions. For the reasons I explain below, neither the '504 and '192 patents nor their file histories support

Hanmi's constructions, but instead reveal that this term should carry the same meaning as "alkaline salt" in the '504 patent.

64. The '192 patent states in column 1, before the "Field of the Invention" section:

> The description of salt forms of the single enantiomers of omeprazole and the process of making the same is herein incorporated by reference to copending Ser. No. 08/376,512.

Col. 1, ll. 10–13. U.S. Patent Application No. 08/376,512 is the application that issued as the '504 patent. In my opinion, based on this unambiguous statement, a person of ordinary skill would understand that the "pharmaceutically acceptable salts" of the '192 patent are the same as the "alkaline salts" of the '504 patent. Therefore, for all of the reasons stated above in the context of addressing the meaning of "alkaline salt" in the '504 patent claims, the "pharmaceutically acceptable salts" of the '192 patent claims would be understood to be basic salts, that is, ones in which (–)-omeprazole is negatively charged, and would not be limited to the exemplified salts as Hanmi has proposed.

65. I understand that Hanmi has pointed to column 4 of the '192 patent where it states that "the term 'pharmaceutically acceptable salt' refers to both acid and alkaline pharmaceutically acceptable non-toxic salts," which Hanmi cites presumably to support its alternate construction that the salts of the invention include acid addition salts. Col. 4, ll. 14–16. A person of ordinary skill would not read this general definition of "pharmaceutically acceptable salt" as contradicting the statement in column 1 that the "description of salt forms of the single enantiomers of omeprazole" is as detailed in the '504 patent—i.e., alkaline.

66. First, this general definition for "pharmaceutically acceptable salt" appears in the context of a paragraph that is not limited to (–)-omeprazole as the only active pharmaceutical ingredient. Col. 4, ll. 9–19. In fact, this paragraph indicates that "other therapeutic ingredients are especially of interest in the treatment of Helicobacter infections." Col. 4, ll. 16–19. These

"other therapeutic agents" need not be limited to alkaline salts, and may be employed as acid addition salts, thus explaining the reference to acid addition salts in the definition of "pharmaceutically acceptable salts." Given the scope of the paragraph in which the definition for "pharmaceutically acceptable salt" appears, there is no reason to read this definition as mandating that salts of (–)-omeprazole be anything other than "alkaline," as conveyed unambiguously in column 1 by reference to the salts of the '504 patent.

67. Second, as mentioned when addressing the term "alkaline salt" in the '504 patent claims, the '504 patent specification emphasizes "the surprising high stability in alkaline conditions for the compounds of the invention," as contrasted to the "acidic conditions" employed in prior art in unsuccessful efforts to prepare "optically pure [individual enantiomers of] omeprazole." Compare col. 13, l. 31 – col. 14, l. 4 to col. 1, ll. 27–42 (noting that acidic conditions "would be devastating" for the individual enantiomers of the invention). This text would confirm the understanding of a person of ordinary skill, that "pharmaceutically acceptable salts" of (–)-omeprazole are "alkaline salts," just as in the '504 patent.

* * *

68. In view of the above, a person of ordinary skill would understand "pharmaceutically acceptable salt" to mean any basic salt (here, a salt in which (–)-omeprazole is negatively charged) that is suitable for pharmaceutical administration, and to not be limited to the exemplary salt forms in the '504 patent specification or to include acid addition salts.

2. "Consisting essentially of the (–)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole"

69. The term "consisting essentially of the (–)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole" appears expressly or by dependence in asserted claims 1–7, 10–19, 21 and 22 of the '192 patent. I understand that the

Court already construed this term in the manner previously proposed by AstraZeneca. Should the Court decide to revisit the construction of this term, I provide my opinion as to the meaning in the attached Appendix.

* * *

70. I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Dated: November 7th, 2011

By: _____
STEPHEN G. DAVIES